REMARKS

Claims 57 – 68 are pending, with claim 68 having been withdrawn from consideration pursuant to an election of species. Claims 57, 59 and 60 are amended herein. No claims are cancelled or added. Accordingly, after entry of the amendments, claims 57 – 69 are pending, with claim 68 standing withdrawn.

All prior rejections have been withdrawn in favor of new rejections of the pending claims under 35 U.S.C. § 103.

Amendments to the claims

Claims 57, 59 and 60 have been amended to recite broader safinamide dosage ranges. Support for the amendments can be found, *e.g.*, at page 19, lines 4 – 19. No new matter has been added.

Rejections Under 35 U.S.C. § 103(a)

Claims 57 – 64 and 67 have been rejected under 35 U.S.C. § 103 as having been obvious over Chiesi, U.S. Pat. No. 5,017,607 ("Chiesi") and Dostert *et al.*, U.S. Pat. No. 5,236,957 ("Dostert"). Claims 65 and 66 have been rejected under 35 U.S.C. § 103 as having been obvious over Chiesi and Dostert, further in view of Chenard, U.S. Pat. No. 6,258,827 ("Chenard").

Chiesi discloses the use of levodopa methyl ester ("LDME"), a levodopa prodrug, in the treatment of idiopathic Parkinson's disease, optionally in combination with selective MAO-B inhibitors, such as deprenyl. Chiesi does not disclose the use of safinamide. Dostert discloses the treatment of idiopathic Parkinson's disease with safinamide[1], which is identified as a "potent inhibitor of monoamine oxidase (MAO), but "does not teach the coadministration of L-Dopa which is administered in an amount that alone has therapeutic effect," Office action, page 5. Citing to *In re Kerkhoven*, the Examiner argues that it would have been *prima facie* obvious "to

[1] A divisional, U.S. Pat. No. 5,502,079 (of record), *claims* methods of treating Parkinson's disease with safinamide.

combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, " that "it would have been obvious to ... have combined L-dopa (with or without [a] decarboxylase inhibitor) with safinamide in the treatment of Parkinson's disease." Office Action, page 6.

Applicants traverse.

Chiesi explicitly teaches that the addition of an MAO-B inhibitor to therapy with levodopa methyl ester "allow[s] a remarkable reduction in the dose of LDME necessary to control the disease, consequently decreasing side effects...." Chiesi, col. 3, lines 9 – 16. The reference is thus fairly read as ***teaching away*** from combination therapies in which L-dopa (or prodrug thereof) is administered "in an amount that alone has therapeutic effect," as required by applicants' claims.[2]

That MAO-B inhibitors permit remarkable reductions in L-dopa dosage is not a remarkable observation, nor original to Chiesi: inhibition of central catabolic pathways has long been known to permit effective concentrations of L-dopa (and thus, of dopamine) to be achieved in brain using lower administered dosages of L-dopa; indeed, a primary purpose of adjunctive administration of MAO-B inhibitors is to permit just such dosage reduction, with concomitant reduction of side effects.

Safinamide, however, is not simply a selective MAO-B inhibitor – it also blocks voltage-sensitive sodium channels, inhibits glutamate release, and blocks dopamine uptake, Caccia *et al.*, "Safinamide: from molecular targets to a new anti-Parkinson drug," *Neurology* 67 (suppl. 2):S18-S23 (2006) [3] – and has therapeutic effects in Parkinson's disease beyond those accounted for by MAO-B inhibition, Stocchi *et al.*, "Symptom relief in Parkinson disease by safinamide: biochemical and clinical evidence of efficacy beyond MAO-B inhibition," *Neurology* 67 (suppl

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[2] Proceeding contrary to accepted wisdom in the art is of course evidence of *non*obviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

[3] Attached hereto as Exhibit A.

2):S24-S29 (2006) ("Stocchi").[4] As a consequence, safinamide can be added to a stable and therapeutically effective L-dopa regimen, providing additional symptomatic benefit. This would neither have been predicted nor reasonably expected from the prior art.

> Stocchi reports the results of an open-label study of safinamide as an add-on to levodopa.
>
> In association with levodopa, ... [100, 150, 200 mg po QD] doses of safinamide induced a significant decrease in motor fluctuations (UPDRS part IV, 2.1 points; $P < 0.001$).... Because MAO-B was fully inhibited (95%) at all doses tested, we suggest that these biochemical and symptomatic dose-dependent effects must be related to additional mechanisms of action, such as inhibition of glutamate release, increased dopamine release, or inhibition of dopamine reuptake.

Stocchi, Abstract. These results were achieved against a background of "**pre-existing optimal** [levodopa] **treatment regimen**...." Stocchi, S29, col. 1 (emphasis added).

Reduction in "off" time in the setting of optimal levodopa treatment is an important therapeutic benefit: prior to addition of safinamide, the study patients "were suffering from motor fluctuations while receiving a stable dosage of L-dopa (plus a decarboxylase inhibitor)," Stocchi, S25, col. 1.

In addition to the statistically significant reduction in motor fluctuations and dyskinesias, which are side effects of levodopa therapy, a beneficial trend was observed with respect to scores on UPDRS Part III, which measures the primary motoric dysfunction of Parkinson's disease.[5] Stocchi, S27, col. 1.

The beneficial trend in UPDRS III scores first reported in Stocchi has now been confirmed, and demonstrated to reach statistical significance, in a 24 week, multi-center, randomized, double-blind, placebo-controlled study. Meshram *et al.*, "Safinamide as add-on to levodopa improves motor function without worsening dyskinesia in patients with mid-late

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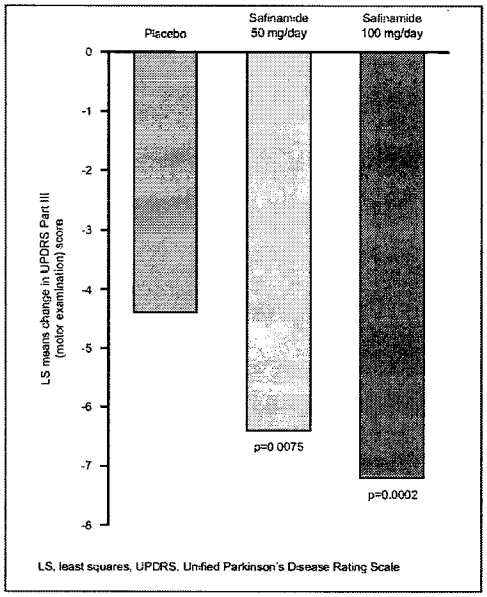
[4] Attached hereto as Exhibit B (already of record). This post-filing date publication includes among its authors two of the instant inventors and reports results from clinical trials sponsored by the owner of the instant application, Newron Pharmaceuticals SpA.

[5] UPDRS Part III measures severity of motor signs, the fundamental motor symptoms of the disease itself, including tremor, facial and generalized bradykinesia, and further includes performance measures on several tasks are used to rate disease severity.

Parkinson's disease," Poster 359, Movement Disorder Society 14th International Congress, Buenos Aires, Argentina, 13-17 June 2010 ("Meshram").[6]

As reported by Meshram, both doses of safinamide (50 mg/day and 100 mg/day), when added to a stable dose of levodopa – a dose that had been clinically optimized prior to study entry – "were associated with significant improvements in UPDRS Part III (motor examination) scores versus placebo (Figure 3)":

Figure 3. Least squares means change in UPDRS Part III (motor examination) total scores between baseline and Week 24



No other drug has been demonstrated to provide motor benefits additional to those seen with optimal doses of levodopa, the gold standard for Parkinson's disease treatment.

These results could not have been predicted from safinamide's known MAO-B inhibitory activity. As noted by Stocchi, safinamide efficacy increases at doses above that required for complete MAO-B inhibition, "results ... [that] support the hypothesis that MAO-B inhibition is a minor contributor to the symptomatic effect of safinamide in PD." Stocchi, p. 28, col. 2.

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6 Attached hereto as Exhibit C. As noted on the Poster, "This study was funded by Newron and Merck Serono SA-Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany." Newron is the owner of the instant application, and Merck Serono is a licensee.

And although Stocchi speculate that, "glutamate release inhibition should occur at the doses used," the authors continue that "its exact role is still under investigation." Stocchi, S28 col. 2 – S29,col. 1. Furthermore, even if safinamide's motoric benefits as an add-on to levodopa were ultimately to be attributed to its glutamate release inhibitory properties, the reported results would not have been expected: "[a]ll the clinically available putative anti-glutamate drugs have thus far failed to demonstrate motor improvement in clinical trials," Stocchi, S 29, col. 1. *See, e.g.*, Rascol *et al.*, "A 2-year, multicenter, placebo-controlled, double-blind, parallel group study of the effect of riluzole on Parkinson's disease progression," *Movement Disorders*, 17 (Suppl. 5), S29 (2002).[7]

Furthermore, the same double-blind study reported in Meshram demonstrates that addition of safinamide to clinically optimized stable doses of levodopa also improves symptoms of depression, a non-motor symptom seen often in mid- to late-stage Parkinson's disease, with improvements reaching statistical significance at 100 mg/day safinamide. Borgohain *et al.*, "Effect of safinamide on depressive symptoms in patients with mid-late stage Parkinson's disease," Poster 324, Movement Disorder Society 14th International Congress, Buenos Aires, Argentina, 13-17 June 2010 ("Borgohain") (attached hereto as Exhibit E). Nothing in Dostert or Chiesi would have predicted these results.

Neither Dostert nor Chiesi would properly have motivated methods of treating Parkinson's disease with safinamide as an add-on to dosages of L-dopa that alone have therapeutic effect – thus vitiating the purported *prima case* of obviousness. In addition, the results of so doing were unexpected, and unexpectedly superior to results previously achieved, providing clear and compelling secondary evidence of nonobviousness. The claimed invention is nonobvious and the rejections should be withdrawn.[8]

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[7] Attached hereto as Exhibit D.

[8] Chenard is added as a tertiary reference in rejection of claims 65 and 66 for its teaching of the adjunctive use of COMT inhibitors, such as tolcapone or entacapone. With failure of the primary and secondary reference to motivate the use of safinamide as an "add-on" to doses of levodopa that "alone

CONCLUSION

Claims 57 – 68 are pending, with claim 68 currently withdrawn from prosecution

The sole rejections remaining in this application, rejection of claims 57 – 67 under 35 U.S.C. § 103, have been traversed. The rejections are in error, and should be withdrawn.

Rejoinder

Claim 57 is generic to the species of "Parkinson's disease agent" previously elected for prosecution on the merits, L-Dopa. Claim 57 recites:

> A method of treating idiopathic Parkinson's disease, comprising:
>
> orally administering safinamide, or a pharmaceutically acceptable salt thereof, on a daily dosage schedule of about 0.5 mg/kg/day to about 2 mg/kg/day to a patient with idiopathic Parkinson's disease; and
>
> concurrently administering to the patient at least one Parkinson's disease agent, wherein the at least one Parkinson's disease agent is selected from the group consisting of L-Dopa and Dopamine agonists, and wherein the at least one Parkinson's disease agent is administered in an amount that alone has therapeutic effect.

No rejections having been predicated on the combination of safinamide with a dopamine agonist, generic claim 57 is allowable. Pursuant to 37 C.F.R. §§ 1.141 and 1.146, rejoinder and allowance of claim 68, drawn to the patentably distinct species of concurrent therapy with safinamide and Dopamine agonists, is appropriate.

Interview request

If the Examiner finds that any matters remain outstanding that preclude allowance, the Examiner is requested to contact applicants' attorney, Daniel M. Becker, at (650) 813-4874, to schedule a personal interview.

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have therapeutic effect," the tertiary reference cannot save the *prima facie* case, nor rebut the compelling secondary indicia of nonobviousness.

Fees

No fees are believed to be due in connection with this response. However, the Director is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 (**Order No.** 373987-011 US (102895)).

Respectfully submitted,

Date: 15 JUNE 2010

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Exhibit A: Caccia *et al.*, "Safinamide: from molecular targets to a new anti-Parkinson drug," *Neurology* 67 (suppl. 2):S18-S23 (2006)

Exhibit B: Stocchi *et al.*, "Symptom relief in Parkinson disease by safinamide: biochemical and clinical evidence of efficacy beyond MAO-B inhibition," *Neurology* 67 (suppl 2):S24-S29 (2006) (already of record)

Exhibit C: Meshram *et al.*, "Safinamide as add-on to levodopa improves motor function without worsening dyskinesia in patients with mid-late Parkinson's disease," Poster 359, Movement Disorder Society 14th International Congress, Buenos Aires, Argentina, 13-17 June 2010.

Exhibit D: Rascol, *et al.*, "A 2-year, multicenter, placebo-controlled, double-blind, parallel group study of the effect of riluzole on Parkinson's disease progression," Movement Disorders, 17 (Suppl. 5), S29 (2002)

Exhibit E: Borgohain *et al.*, "Effect of safinamide on depressive symptoms in patients with mid-late stage Parkinson's disease," Poster 324, Movement Disorder Society 14th International Congress, Buenos Aires, Argentina, 13-17 June 2010 ("Borgohain") (attached hereto as Exhibit E).

NEUROLOGY 2006;67:S18-S23

Safinamide

From molecular targets to a new anti-Parkinson drug

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Abstract.

Ideal treatment in Parkinson's disease (PD) aims at relieving symptoms and slowing disease progression. Of all remedies, levodopa remains the most effective for symptomatic relief, but the medical need for neuroprotectant drugs is still unfulfilled. Safinamide, currently in phase III clinical trials for the treatment of PD, is a unique molecule with multiple mechanisms of action and a very high therapeutic index. It combines potent, selective, and reversible inhibition of MAO-B with blockade of voltage-dependent Na^+ and Ca^{2+} channels and inhibition of glutamate release. Safinamide has neuroprotective and neurorescuing effects in MPTP-treated mice, in the rat kainic acid, and in the gerbil ischemia model. Safinamide potentiates levodopa-mediated increase of DA levels in DA-depleted mice and reverses the waning motor response after prolonged levodopa treatment in 6-OHDA-lesioned rats. Safinamide has excellent bioavailability, linear kinetics, and is suitable for once-a-day administration. Therefore, safinamide may be used in PD to reduce l-dopa dosage and also represents a valuable therapeutic drug to test disease-modifying potential.

Parkinson's disease (PD) is a progressive neurodegenerative syndrome that begins insidiously and gradually worsens in severity. The neurodegenerative processes result from the loss of dopaminergic (DA) neurons that project into the striatum from the substantia nigra pars compacta, leading to the motor symptoms of the disease.[1] The reasons for this neuron loss remain unknown, and although specific genes, including α-synuclein and parkin, have been identified as causal in several patients,[2,3] it is likely that the majority of PD cases are a result of both genetic and environmental factors.[4] The early motor symptoms and signs of PD, i.e., resting tremor, bradykinesia, and rigidity, are usually treated with levodopa and DA agonists. As PD progresses over time, symptoms that do not respond to levodopa develop, such as fluctuations in motor performance, the freezing phenomenon, and loss of postural reflexes. These are often referred to as non-DA-related features of PD. Moreover, bradykinesia that responded to levodopa in the early stage of PD increases as the disease worsens and no longer fully responds to levodopa.[5]

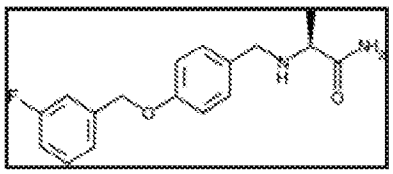
Significant advances have been made in understanding the molecular and cellular factors involved in the pathogenesis of PD, but satisfactory approaches to relieve late symptoms and to slow the progression of the disease (i.e., protecting DAergic neurons from premature death) have not been developed. Although promising results have been obtained experimentally with several classes of drugs,[6,7] none of the current treatments has been clinically proved to arrest or even delay neuron loss in PD.

Current symptomatic treatment relies on such agents as levodopa, DA agonists, MAO-B inhibitors, and catechol-*O*-methyltransferase (COMT) inhibitors that compensate for the deficit in the nigrostriatal DAergic input pathways, but it is now accepted that several other events contribute to disease progression. These include oxidative stress with free radical production,[8] neuroinflammation,[9] alterations in the ubiquitin-proteasome system leading to apoptosis,[10] mitochondrial dysfunctions,[11] and excitotoxicity mediated by excessive glutamate release.[12] Novel drugs combining multiple biochemical actions may have both symptomatic and neuroprotective effects. In this regard, safinamide is a new molecule with multiple mechanisms of action and experimental evidence supporting clinical trials to confirm its symptomatic and neuroprotecting potential.

Pharmacodynamic properties.

Safinamide, (S)-(+)-2-[4-(3-fluorobenzyloxy-benzylamino) propion-amide] (figure 1) is a small molecule, chemically and metabolically stable, and water soluble, combining low CNS toxicity and multiple mechanisms of action. These include specific and potent modulation of DA metabolism, blockade of Na^+/Ca^{2+} channels, and inhibition of glutamate release. The unique combination of these properties offers the potential of combining symptomatic relief (by DA modulation) and neuroprotection (by Na^+/Ca^{2+} and glutamate release blockade) in PD.

Figure 1. Chemical structure of safinamide.



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Effects on monoamine metabolism. MAO is a key enzyme in the catabolism of DA, leading to the formation of potentially toxic byproducts within nigral neurons and in the adjacent glia. Along with this oxidation step, some free radicals and other reactive oxygen species are generated, resulting in oxidative stress and eventually in neuron death. In monkey and human brain, DA is preferentially (more than 80%) metabolized by MAO-B. With MAO-B inhibited, the oxidative deamination of both endogenous and exogenous levodopa-derived DA decreases and DA levels increase with restored dopaminergic function.[13] In addition, MAO-B inhibition may prevent activation of toxins and free radicals formed by oxidative steps, possibly reducing the progression of neurodegenerative processes.[14,15] Safinamide is a highly selective MAO-B inhibitor in rat brain mitochondria, with an IC_{50} of 98 nM. It is about 5000-fold more potent in inhibiting MAO-B versus MAO-A (figure 2A). With the same potency, safinamide inhibits MAO-B in human brain and is even more potent in inhibiting MAO-B in human platelets, with an IC_{50} of 9 nM (figure 2B). Unlike clinically used MAO-B inhibitors, enzyme inhibition by safinamide is reversible. It is not dependent on preincubation time between the enzyme and the inhibitor, as shown by no difference between IC_{50} values with or without preincubation (figure 2C). This means that enzyme inhibition is immediately reached after enzyme/inhibitor complex formation without need for a covalent binding, as is typical for irreversible inhibition.

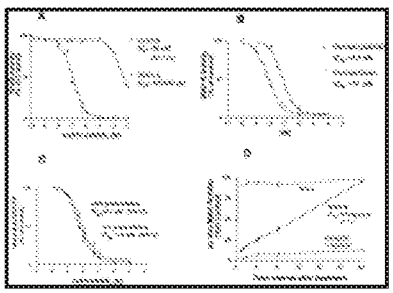

Figure 2. In vitro and in vivo effects of safinamide on MAO enzyme activity: (A) In vitro effects on MAO-A and MAO-B in rat brain mitochondria. (B) In vitro effects on MAO-B in human platelets and brain. (C) Time-dependent effect on MAO-B in human platelets. (D) In vivo effects on MAO-A and MAO-B after oral treatment; comparison with rasagiline.

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In ex vivo experiments after oral treatment, safinamide dose-dependently inhibits mouse brain MAO-B, leaving MAO-A virtually unaffected. MAO-B activity recovers quickly, starting from 8 hours, suggesting that in vivo safinamide is a specific and short-acting MAO-B inhibitor, as expected

of a reversible inhibitor. Conversely, rasagiline's long-lasting inhibition of MAO-B does not show recovery up to 24 hours, as is typical of irreversible inhibitors (figure 2D).

The MAO-B inhibitory effect of safinamide was also found in plasma-rich platelets of healthy volunteers after a single series of ascending oral doses (25 to 2500 μg/kg). Complete inhibition (90%) was seen at 600 μg/kg with an ED_{50} of 87 μg/kg (figure 3). After chronic administration in cynomolgus monkeys (13 weeks, 10 and 20 mg/kg orally), safinamide at 24 hours after the last treatment significantly increased brain DA levels (27% and 48%, respectively), with a concomitant decrease of the metabolite dihydroxyphenylacetic acid (–19% and –41%, respectively) in the putamen. In parallel, MAO-B was found significantly inhibited.

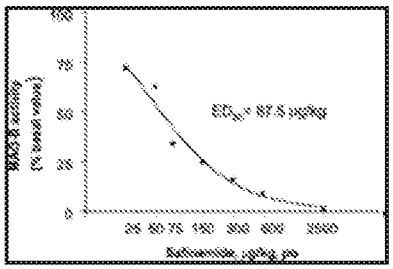

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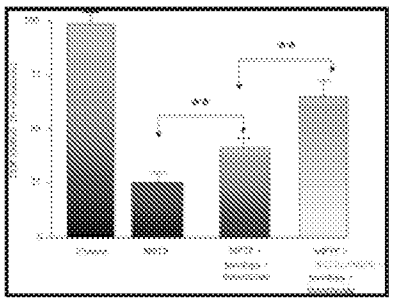
Figure 3. Effect of single ascending oral dose of safinamide on platelet MAO-B activity in healthy volunteers.

After 39 weeks of treatment, the magnitude of the DA increment was similar to that found after 13 weeks, indicating that safinamide does not induce tolerance even after chronic treatment. In the same safinamide-treated animals, hippocampal levels of serotonin and its metabolite and cortical levels of norepinephrine (both produced by MAO-A-mediated catabolism) were not affected.

Biochemical and pharmacologic effects in animal models. Safinamide was tested in different animal models of PD, such as add-ons to levodopa in DA-depleted animals, the "wearing-off" model in denervated levodopa-treated rats,[16] and the *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model.

Add-on to levodopa in DA-depleted mice. Physiologically, DA catabolism in rodent brain is primarily MAO-A-mediated. In fact, safinamide up to 80 mg/kg orally had no effect on striatal DA metabolism in rats. As shown in figure 4, in DA-depleted C57BL mice (15 days after MPTP treatment), safinamide (20 mg/kg IP) significantly increases DA levels (60%) when coadministered with levodopa (100 mg/kg IP + benserazide 12.5 mg/kg IP). Safinamide does not inhibit COMT activity in vitro or in vivo.

*Figure 4. Effect of safinamide on brain DA levels in levodopa-treated C57BL mice (15 days after MPTP). **P < 0.01.*



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These findings agree with the hypothesis that deamination of DA by glial MAO-B becomes more prominent when catabolism by MAO-A in the dopaminergic nerve terminals has been compromised, such as in the MPTP model, and strongly support the use of safinamide as add-on therapy with levodopa in PD patients.

"Wearing-off" model in denervated levodopa-treated rats. In 6-hydroxydopamine (6-OHDA)-lesioned rats, turning evoked by injection of the same dose of levodopa decreases after chronic treatment (25 mg/kg IP for 28 days). In particular, the duration of rotations becomes significantly shorter during the course of levodopa treatment, mimicking the "wearing-off" phenomenon observed in PD patients. At time of appearance of this motor complication there is a consistent imbalance between dopaminergic and glutamatergic systems in favor of an increased excitatory input.[16] Using this model, we showed that on day 29 the decreased response to levodopa is reversed by single co-administration of safinamide (20 mg/kg IP). This effect is more pronounced than that obtained with the glutamate antagonist MK-801 (figure 5).

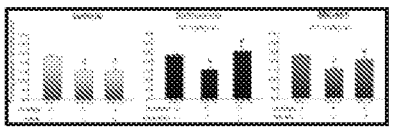

Figure 5. Effect of safinamide on the rotational response to chronic levodopa in 6-OHDA-lesioned rats. $^{\$}P < 0.05$ vs levodopa on day 1; $^{*}P < 0.05$ vs levodopa on day 28.

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The potentiation of the levodopa response supports the hypothesis of additional neuroprotective mechanisms beyond restoration of DA levels in the antiparkinson activity of safinamide. Inhibition of glutamate release is likely to be one of them.

MPTP model in mice (prophylactic schedule). Fifteen days after injection, the meperidine derivative MPTP causes severe DA depletion and cell death of nigrostriatal dopaminergic neurons. By MAO-B, MPTP is converted to its toxic metabolite MPP^{+}. Blockade of this reaction prevents MPTP neurotoxicity. Given before MPTP, safinamide at all doses tested inhibits striatal DA depletion and

preserves nigral cell death by blocking MAO-B, as detected immunohistochemically by counting tyrosine hydroxylase-positive neurons (data not shown).

Effect on sodium and calcium channels. Safinamide has high affinity for the Na^+ channel-binding site II in rat cortical membranes, with an IC_{50} of 8 μM. The binding site II is a specific binding site internal to the channel pore where drugs with blocking activity bind. Safinamide has no affinity for more than 80 different types of receptors, such as dopamine, glutamate, adenosine, serotonin, muscarinic, and nicotinic, as well as GABA.

Binding to the Na^+ channel is functionally active. In fact, safinamide inhibits the fast Na^+ currents in a concentration- and state-dependent manner (different potency at different states of the channel) in rat cortical neurons, as assessed by patch clamp. At depolarized membrane potentials, when a large number of channels are in the inactivated state mimicking neuronal pathologic conditions, safinamide is three times more potent (IC_{50} 33 μM) than at resting potential (IC_{50} 96 μM), suggesting a preferential interaction with the inactivation state of the channel. Therefore, in the presence of safinamide a much higher proportion of Na^+ channels is kept in the inactivated state and prevented from activating. The state-dependent blockade is also confirmed using a cell line transfected with the sodium subtype Nav1.3, the most abundant sodium channel subtype in the brain.

In addition, the blockade of Na^+ currents by safinamide is use-dependent, meaning an enhancement of the blockade during high-frequency stimulation when there is a large accumulation of channels in the inactivated state. Functionally, the use-dependent blockade results in depression of neuronal activity at high-frequency firing and ineffectiveness at a normal firing rate, suggesting that safinamide will selectively depress abnormal activity, leaving unaffected the physiologic activity and thus avoiding CNS depressant effects.

Safinamide inhibits the action potential firing in cortical neurons, slowing recovery from the inactivation state and thus reducing channel availability for subsequent Na^+ spikes.

Safinamide blocks N-Type Ca^{2+} currents in rat cortical neurons (IC_{50} 23 μM), suggesting that it might participate in the inhibition of neurotransmitter presynaptic release (e.g., excitatory amino acids), mostly influenced by the activation of N-type Ca^{2+} channels. In vivo, peripheral L-type Ca^{2+} channels are not affected by safinamide, as demonstrated by no effects per se on blood pressure and heart rate or on the pressor response to norepinephrine in the pithed rat up to 50 mg/kg IP.

Effect on glutamate. Safinamide inhibits glutamate release induced by depolarizing conditions in rat hippocampal synaptosomes (IC_{50} 9 μM). At high K^+ concentrations, the release of the neurotransmitter is Ca^{2+}-mediated. Therefore, safinamide, by blocking N-Type Ca^{2+} mobilization, inhibits glutamate release, one of the most relevant excitotoxic inputs leading to neuron death.

Pharmacologic effects in neuroprotection/neurorescuing models. Taking into account the Na^+/Ca^{2+} channel and glutamate release inhibitory properties, safinamide was investigated in several in vitro and in vivo models of neuroprotection not attributable to MAO-B-related mechanisms.

In vitro veratridine-induced neuron cell death. The prolonged opening of veratridine-sensitive Na^+

channels in neuron cultures results in Ca^{2+}-dependent cell degeneration. The damage can be prevented by Ca^{2+} and/or Na^{+} blockers. In rat primary cortical neurons, safinamide, added 1 hour before veratridine, reduces the neuron damage with an IC_{50} 1.4 μM (figure 6), supporting that the functional blockade of opening voltage-dependent Na^{+} and Ca^{2+} channels results in neuroprotection.

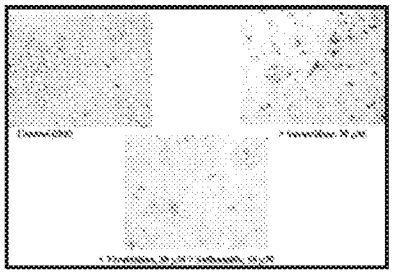

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Figure 6. Effect of safinamide on veratridine-induced cell death in rat cortical neurons.

MPTP model in mice (therapeutic schedule). Prevention of neuron death observed with a compound administered after MPTP suggests a neuroprotective mechanism independent of MAO-B inhibition. When given 4 hours after MPTP (radiochemical HPLC detection studies have shown that 4 hours after [^{14}C]-methyl-MPTP administration to mice, the conversion of MPTP to MPP^{+} by MAO-B is complete), safinamide does not prevent the striatal DA decrease, which reflects the acute action of MPP^{+} taken up by the terminals, but significantly inhibits cell body degeneration in the substantia nigra pars compacta (figure 7). These results demonstrate that safinamide is endowed with neuroprotectant mechanisms in addition to MAO-B inhibition.

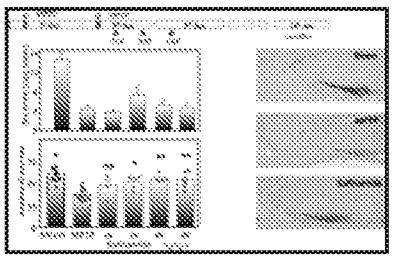

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*Figure 7. Neurorescuing effect of safinamide administered 4 hours after MPTP on nigral dopaminergic neurons in C57BL mice. *P < 0.05 vs MPTP; **P < 0.01 vs MPTP.*

Kainic acid model in rats. Seven days after injection, kainic acid, a rigid analogue of glutamate, induces neuronal hippocampal degeneration. Safinamide administered 15 minutes before kainic acid protects against hippocampal neuron loss, starting at 10 mg/kg showing neuroprotective properties (figure 8).

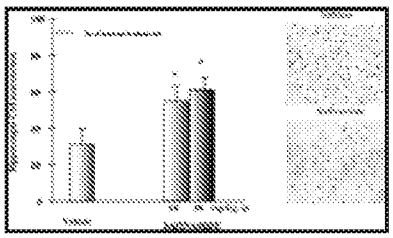

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*Figure 8. Neuroprotective effect of safinamide on hippocampal neuronal cell loss induced by kainic acid in rats. *P < 0.05 vs vehicle. Note the neuron loss in the vehicle-treated rats, while rats pretreated with safinamide show little evidence of damage, as shown by the abundance of normal healthy cells with clear cytoplasm.*

Ischemia model in gerbils. Bilateral carotid occlusion (BCO) in mongolian gerbils is an accepted model of transient ischemia resulting in hippocampal neuron loss. In a first series of experiments, safinamide (100 mg/kg IP) was administered 30 minutes before and after BCO. The neuron damage is almost completely prevented by safinamide (figure 9). To better define the time frame of the protective effect, in a second series of experiments safinamide was given at different times only after BCO. In this protocol, safinamide shows a relevant neurorescuing effect on hippocampal neurons when given 3 hours after ischemia (figure 10).

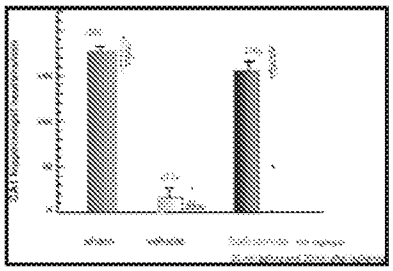

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*Figure 9. Neuroprotective effect of safinamide on ischemia-induced hippocampal neuron death in gerbils. **P < 0.01 vs sham.*

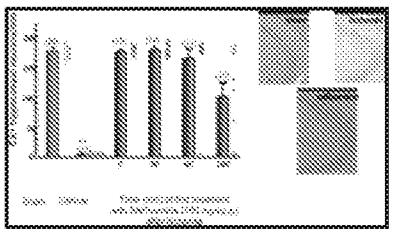

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Figure 10. Neurorescuing effect of safinamide on ischemia-induced hippocampal neuron death in gerbils. P < 0.01 vs sham.

Pharmacokinetic properties. Preclinical pharmacokinetic studies were performed in mice, rats, and

monkeys after administration of safinamide given as a single IV or oral dose or as daily multiple oral doses. Safinamide has a high oral bioavailability (80–92%), is rapidly absorbed and, in plasma, after reaching the peak within 0.5–2 hours declines, with a terminal half-life of about 3, 7, and 13 hours in mice, rats, and monkeys, respectively. Brain levels of safinamide are always higher than the corresponding plasma concentrations, with a brain to plasma ratio of 16, 16, and 9 in mice, rats, and monkeys, respectively. At current pharmacologic doses, the brain levels of safinamide are expected to be in the high μM range.

Assuming the same brain:plasma ratio known for monkeys, plasma levels of 5–6 μM that are seen in humans at steady state after 7 days of an oral dose of 150 mg should correspond to brain level of 40–50 μM. Therefore, all pharmacodynamic properties of safinamide should be at play with clinically used doses and expected to concurrently exhibit their effects.

Conclusions.

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Safinamide, currently in phase III trials for the treatment of PD and in phase II trials for epilepsy, is a unique molecule with multiple mechanisms of action and with a very high therapeutic index. It combines potent, selective, and reversible inhibition of MAO-B with voltage-dependent Na^+ and Ca^{2+} channel blockade and glutamate release inhibition.

Safinamide has neuroprotective and neurorescuing effects in the mouse MPTP model, in the rat kainic acid model, and in the gerbil ischemia model, potentiates levodopa-mediated increase in DA levels in DA-depleted mice, and reverses the motor response complications of long-term L-dopa treatment in 6-OHDA-lesioned rats. Safinamide has an excellent bioavailability, linear kinetics, and a long half-life. It is very safe, well tolerated, and suitable for once-a-day administration.

All the pharmacodynamic properties are manifested at concentration that should be easily reached in the ongoing clinical trials. Therefore, safinamide might be used in PD to reduce levodopa dosage. Furthermore, it represents a valuable test to assess the clinical validity of experimental mechanisms that are expected to modify disease progression.

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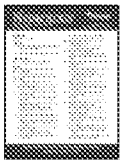

F. Stocchi, L. Vacca, P. Grassini, M. F. De Pandis, G. Battaglia, C. Cattaneo, and R. G. Fariello

Symptom relief in Parkinson disease by safinamide: Biochemical and clinical evidence of efficacy beyond MAO-B inhibition

Neurology, October 10, 2006; 67(7_suppl_2): S24 - S29.

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Symptom relief in Parkinson disease by safinamide

Biochemical and clinical evidence of efficacy beyond MAO-B inhibition

F. Stocchi, MD, PhD; L. Vacca, MD, PhD; P. Grassini, MD; M.F. De Pandis, MD, PhD; G. Battaglia, MD; C. Cattaneo, PhD; and R.G. Fariello, MD

Abstract—In an open pilot study, doses of safinamide (100, 150, and 200 mg once a day, higher than previously tested) were administered to 13 parkinsonian patients along with a stable dose of dopamine (DA) agonist, causing a significant progressive improvement in motor performance as evaluated by the Unified Parkinson Disease Rating Scale (UPDRS) part III over an 8-week period (4.2 points; $P < 0.001$). In association with levodopa, the same doses of safinamide in another group of patients (N = 11) induced a significant decrease in motor fluctuations (UPDRS part IV, 2.1 points; $P < 0.001$), accompanied by a dose-proportional increase of the levodopa AUC, up to 77% from baseline. Because MAO-B was fully inhibited (95%) at all doses tested, we suggest that these biochemical and symptomatic dose-dependent effects must be related to additional mechanisms of action, such as inhibition of glutamate release, increased dopamine release, or inhibition of dopamine re-uptake. These hypotheses are under investigation and will pursue confirmation in controlled clinical trials.

NEUROLOGY 2006;67(Suppl 2):S24–S29

Safinamide is a benzylamino derivative with anticonvulsant,[1] antiparkinson,[2] and neuroprotectant[3,4] properties. Safinamide blocks Na and Ca channels in a use- and frequency-dependent manner with an EC_{50} at around 20–30 μM; it also inhibits glutamate release (EC_{50} 10 μM).[5] In addition, safinamide is a potent reversible and highly specific MAO-B inhibitor,[6] providing complete platelet MAO-B inhibition in humans at serum levels ≥0.5 μg/ml without affecting MAO-A at doses 20 times higher.[7] In a recent double-blind placebo-controlled study,[8] two doses of safinamide (mean and median doses of 40 and 70 mg/day) were administered for 3 months to moderately ill PD patients. The higher dose (calculated to be in the range that would block glutamate release and ion channels) provided significant improvement in all preset efficacy end points. The lower dose (calculated to provide complete MAO-B inhibition) resulted only in a trend toward efficacy. These results suggested that MAO-B inhibition was only one component of safinamide's therapeutic efficacy and that patients under treatment with a stable dose of one DA agonist responded better than treatment-free patients. This latter feature was postulated to be the result of combined D1 and D2 receptor stimulation. The commercially available agonists mostly stimulate D2 receptors, whereas safinamide should induce a significant elevation of endogenous DA, the natural ligand of both D1 and D2, resulting in a levodopa-like clinical effect.

A pilot study was therefore designed to seek further evidence that higher safinamide doses may cause greater symptomatic improvement and that MAO-B inhibition is only a small component in safinamide's symptomatic effect. In addition, the effects of escalating safinamide doses added to levodopa both on symptoms and on levodopa, DA, and DA metabolite serum levels were explored.

Methods. This was an open pilot single-center study. Safinamide was administered orally for 6 consecutive weeks to informed and consenting PD patients starting with the initial dose of 100 mg once a day and increasing to 150 and 200 mg by two 2-week steps, then entering a 2-year treatment at the high-

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est tolerated dose. The protocol was approved by the institution's Ethics Committee.

Inclusion criteria. Two groups of patients were studied. Group 1 consisted of white males and females ≥30 years of age who were affected by idiopathic PD, Hoehn and Yahr stages III-IV and were suffering from motor fluctuations while receiving a stable dosage of L-dopa (plus a decarboxylase inhibitor). Patients enrolled in group 2 were taking single DA agonist monotherapy for at least 4 weeks before the screening visit. All were willing to participate and were able to understand and sign the approved Informed Consent form.

Exclusion criteria. Women of childbearing potential, history of alcohol or drug abuse, presence of an ongoing pathologic process other than PD, history of glaucoma, allergic reaction to antiepileptic drugs, previous pharmacologic treatment that might have interfered with safinamide, presence of postural hypotension, or with liver enzyme at screening visit greater than twice the upper limits of normal were excluded. Consumption of foods high in tyramine content was forbidden.

On day 6 of the run-in period, eligible L-dopa-treated patients presented for baseline clinical evaluation (Unified Parkinson Disease Rating Scale, UPDRS; Clinical Global Impression, CGI) and blood sampling collection for measurement of platelet MAO-B activity and levodopa dopamine (DA), dihydroxyphenilacetic acid (DOPAC), homovanilic acid (HVA) levels, to be repeated at 60, 120, 180, and 240 minutes after levodopa intake. On day 7, all patients returned to the clinic for reassessment of UPDRS parts II, III, and IV and CGI part I, after which they received the first administration of the test drug and were given a 2-week supply of 50-mg capsules to be taken fasting in the morning, two of them in the first 2 weeks, and then three and four in the successive 2-week periods. Compliance was checked by sampling of safinamide blood levels 3 hours after drug intake at each return visit.

To collect preliminary data on extended tolerability and efficacy, at the end of the 12-week period patients entered a 2-year extension treatment, taking the maximal tolerated dose and being evaluated every 4 months.

Criteria for evaluation. *Efficacy.* Changes in clinical conditions were assessed by performing UPDRS part II, III, and IV dyskinesia scale and the CGI evaluation every second week and were compared to the baseline.

Safety. Safety was assessed by spontaneous reporting of adverse events (AEs) recorded by the patients and by performing hematologic and biochemical tests as well as vital signs, urinalysis, and ECG screening at baseline and every 2 weeks. Visual evoked potentials (VEPs) were performed at baseline and at study end.

Evaluation of biomarkers. MAO-B enzyme activity assay in platelet-rich plasma (PRP). The MAO-B enzyme activity was assessed in PRP by a radioenzyme assay using [^{14}C]-PEA as selective substrate.[9] The enzymatic activity was expressed as pMoles of substrate transformed/mg protein/hour.

Plasma catecholamine levels. The plasma catecholamine levels (DA, dihydroxyphenylacetic acid, homovanillic acid, and levodopa) were measured using HPLC coupled to an electrochemical detector with slight modification from a previously described method.[10]

Statistical analysis. The sample size of 22 evaluable subjects was calculated for detecting a linear trend among the three doses of safinamide in the changes from baseline of total score of UPDRS section III, with the following assumptions: pool standard deviation of 4.2; power of the F-test of 80%; type I error of 5%, $\alpha = 0.05$. The effect of safinamide on the parameters measured by a continuous or discrete scale was analyzed by repeated-measurement analysis of variance (ANOVA) in the Per-Protocol (PP) sample and by ANOVA handled by GLM procedure of SAS in the Intent-To-Treat (ITT) sample. To compare the effect among visits, the polynomial contrasts were adopted to study the linear and quadratic trend. Paired t-test was used to assess the significance of changes from baseline at each treatment visit.

In the presence of dichotomous or categoric variables, the effect on time (doses) of safinamide was analyzed by Friedman's test in the PP sample and by repeated-measurement logistic analysis, handled by the GENMOD procedure of SAS, in the ITT sample and in the safety population.

All comparisons among visits or between groups were two-sided and a P value of 0.05 or less was taken as statistically significant. No adjustment of significance level of multiple comparisons was made to preserve the overall 5% level because of the explorative and descriptive nature of the comparisons.

Results. *Patients disposition.* Twenty-five patients were screened and entered the study, one dropping out after the first test drug administration for unknown reasons. Eleven patients were under levodopa treatment and 14 under treatment with a DA agonist (6 pramipexol, 5 ropinirole, 3 cabergoline). In the former group, patients were older (65.9 ± 10 versus 51.6 ± 8), had worse scoring on CGI I (10 moderately, one markedly ill, versus one borderline, 7 mildly, and 6 moderately ill) and UPDRS-IV (5.12 ± 1.8 versus 1.2 ± 1.2). UPDRS-III was not different in the two groups averaging 16.0 ± 2.8 and 17.1 ± 4.9. Twenty-four patients were at stage III of the Hoen and Yahr scale and one in the levodopa group was at stage IV.

Ten levodopa (one withdrawn for a nonserious AE; see below) and 13 DA agonist patients completed the study. Two of these patients had their levodopa dose decreased by one-third.

Overall, safinamide was well tolerated at all tested doses (table). No serious AEs were reported.

Table Adverse events (AEs) during the study*

AEs by body system and WHO preferred term	L-Dopa		DA agonist		Total	
	n	%	n	%	n	%
Patients exposed to treatments	11	100	14	100	25	100
Psychiatric	1	9.1	6	42.9	7	28.0
Confusion	1	9.1	2	14.3	3	12.0
Visual hallucination			3	21.4	3	12.0
Auditory hallucination			1	7.1	1	4.0
Agitation, nervousness			2	14.3	2	8.0
Insomnia			1	7.1	1	4.0
Libido decrease			1	7.1	1	4.0
Body as whole	2	18.2			2	8.0
Fever	2	18.2			2	8.0
Gastrointestinal			1	7.1	1	4.0
Gastrointestinal pain			1	7.1	1	4.0
Urinary system	1	9.1			1	4.0
Cystitis	1	9.1			1	4.0
Ocular system	1	9.1			1	4.0
Visual disturbances	1	9.1			1	4.0
Skin and appendages	1	9.1			1	4.0
Itchiness	1	9.1			1	4.0

* The DA agonist group had a higher rate of psychiatric symptoms, as expected with these drugs. There was only one AE-related withdrawal, a patient experiencing itching and visual disturbances simultaneously. All AEs were transient and reverted promptly to normal.

All instrumental and laboratory assessments, including VEP, did not reveal abnormalities deemed to be of clinical relevance. One patient dropped out for AE (itching), which promptly resolved. Four episodes of hallucination occurred in association with DA agonists, an event often reported with this class of drugs.

Biochemical markers. The results of platelet MAO-B activity are shown in figure 1. The lowest dose of 100 g/day caused complete (97%) MAO-B inhibition at the first measurement in all patients. Enzyme activity was inhibited to the same degree throughout the study.

Safinamide serum levels. Serum levels of safinamide confirmed good compliance in all patients. Regression analysis showed a significant dose-concentration relationship and linearity to the dose. There were no significant differences between the levels in the levodopa and the DA agonist group (data not shown).

Dopamine and metabolite serum levels. Dopamine levels showed a moderate nonsignificant increase of about 30% compared to the baseline levels. The magnitude of this increment was the same independently of the safinamide dose (figure 2A). The dopamine metabolites DOPAC and HVA did not show statistical variation during safinamide treatment versus the pretreatment period (data not shown).

Levodopa serum levels. The addition of safinamide to levodopa produced a significant progressive augmentation of the levodopa serum AUC ranging from 56% at the dose of 100 mg/day to 88% with 200 mg (figure 2B).

Efficacy. In DA agonist-treated subjects, UPDRS Part II improved from a mean initial value of 6.1 to 5.1 at week 6. When safinamide was associated with

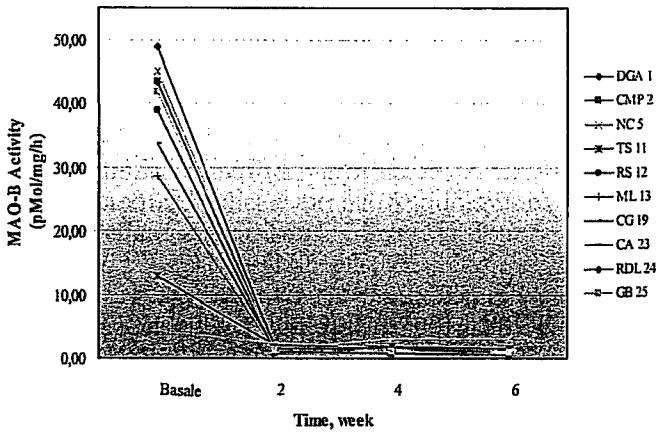


Figure 1. MAO-B activity in plasma PRP in 10 levodopa-treated patients at baseline and after adding incremental doses of safinamide: 100, 150, and 200 mg/day each dose for 2 weeks. From the lowest dose upward there is a <95% enzyme inhibition.

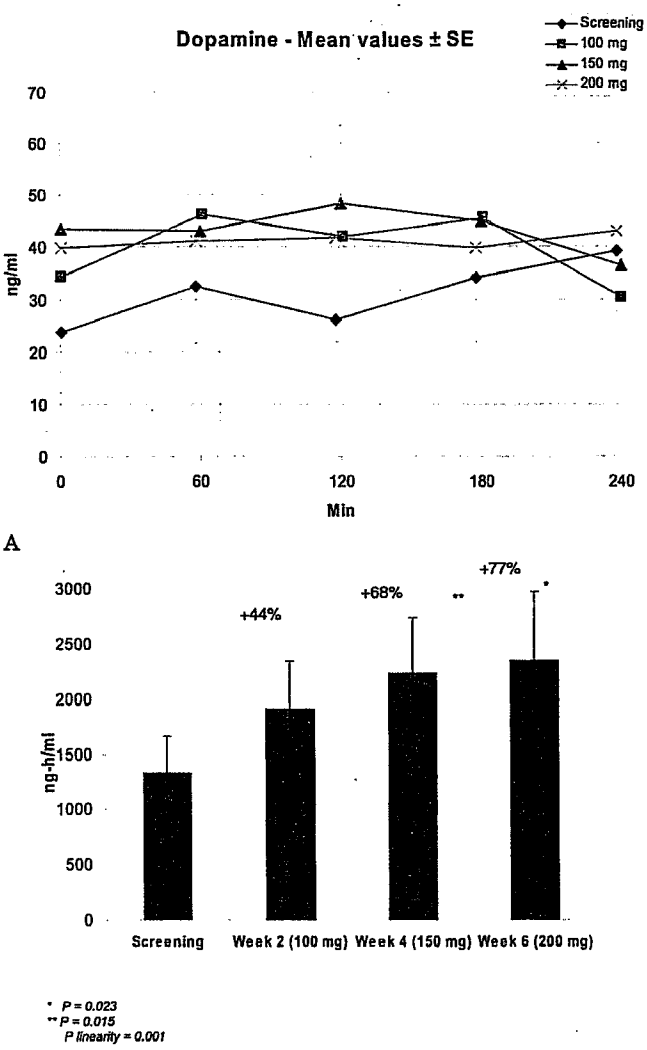


Figure 2. (A) Levels of serum DA measured at baseline and after addition of safinamide 100, 150 and 200 mg /day. Compared to baseline there is a dose-independent stable increment of about 30% that does not reach statistical significance. This effect is interpreted as the effect of peripheral MAO-B inhibition. (B) Area under the curve of serum levodopa levels is increased proportionally to the dose of safinamide added to the treatment, reaching 88% compared to baseline (no safinamide added).

levodopa it decreased from 6.1 to 4.2 at week 6. These results did not reach statistical significance.

A progressive decrease of UPDRS III score was seen in patients receiving a DA agonist (figure 3A).

From a mean baseline of 18.0 points ("on" phase) a decrease was seen to 15.9 after 2 weeks (P [t-test] = 0.02), then 14.6 at week 4 ($P < 0.001$) and 13.8 at week 6 ($P < 0.001$). Levodopa-treated patients did not show a statistically significant decrement but rather an improvement trend starting from 16.3 points, moving to 16.2, at 2 weeks, then 15.1 at 4 weeks ($p = 0.056$), and 14.9 at 6 weeks ($P = 0.054$).

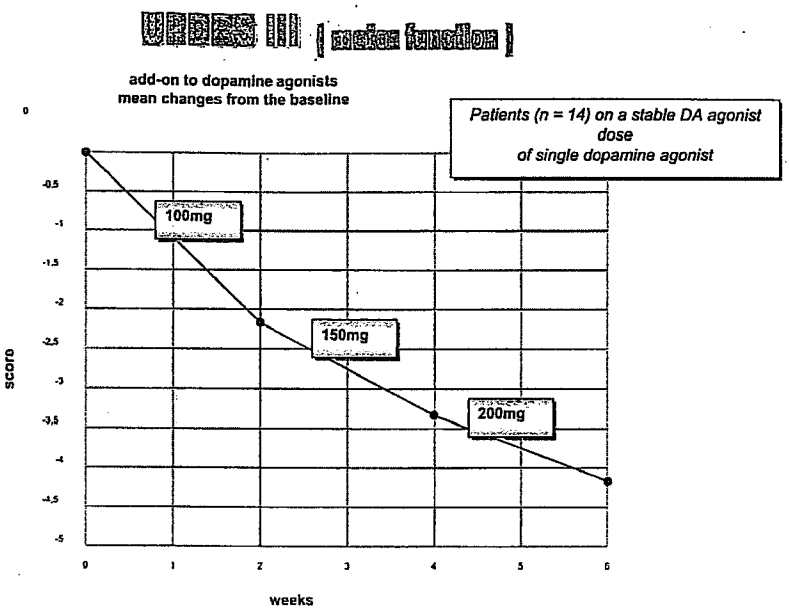
On the contrary, UPRDS IV mirrored the results for part III. Whereas the improvement did not reach statistical significance in DA-agonist treated subjects, levodopa patients performed significantly better after 100 mg (from mean score of 5.1 to 3.9; $P = 0.008$) and even more so after 150 mg (score 3.0; $P < 0.001$), an improvement that was maintained with 200 mg/day (2.9; $P < 0.001$) (figure 3B).

Discussion. Safinamide serum levels were linear and dose proportional in association with both levodopa and DA agonists. In a previous study, linearity and lack of interference between safinamide and antiepileptic drugs was demonstrated at the same dose range.[11] This study therefore suggests lack of metabolic interference between safinamide on the one hand and levodopa and dopamine agonists on the other.

The administration of safinamide at doses equal to or greater than 100 mg/day was very well tolerated and caused a close to 100% inhibition of peripheral MAO-B from the lowest dose upward. In patients under stable treatment with a DA agonist, symptoms improved at each increment of the safinamide dose. This inhibition is likely to have determined the moderate increase of DA levels of about 30% over the baseline, which remained constant under all doses. Therefore, these results further support the hypothesis of symptom-relieving effects by safinamide far beyond MAO-B inhibition.

Assays for determination of levodopa, DA, and metabolite levels gave unexpected results because the levodopa AUC was progressively increased. Peripheral levodopa levels may be raised by inhibiting the main metabolizing enzymes dopadecarboxylase and catechol-*O*-methyl transferase (COMT). Dopa decarboxylase was already inhibited by the presence of benserazide or carbidopa in the levodopa formulations. With COMT inhibitors, variable increases have been reported,[12-15] ranging from 21% to 61%, with the greatest increase reported by Napolitano et al.[15] after 6-week treatment with tolcapone TID. Furthermore, the increase was in parallel with the increment of safinamide doses. The fact that MAO-B was fully inhibited at all doses therefore militates against an unlikely role of MAO inhibition in raising levodopa levels. Based on these results, safinamide was tested in separate studies as a potential COMT and L-dopa decarboxylase inhibitor and was found to be totally inactive. We hypothesize that the putative DA uptake inhibition deriving from safinamide itself, in addition to the one seen as a consequence of MAO-B inhibition, may contribute to this levodopa elevation. Experimental evidence suggests that increased peripheral levodopa signifies increased DA availability to the brain. In parallel with the increased peripheral levodopa, a significant reduction of dyskinesia was observed at the doses of 100 and 150 mg, without further improvement at 200 mg.

The efficacy data must be interpreted with caution, this being an open study. There is no satisfactory substitute for placebo. However, the following facts reinforce an optimistic interpretation of the results even under the present study limitations. (a) The data are remarkably similar to those obtained in



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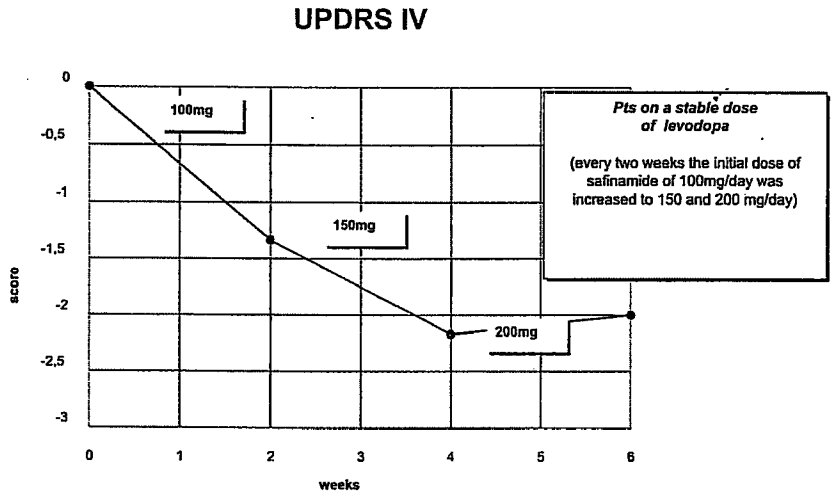

B

Figure 3. Mean changes of UPDRS scores (point variations on the ordinate) in patients after addition of increasing doses of safinamide. Significant (see text for statistics) and progressive decrease of UPDRS-III in addition to DA agonists (upper part, A) and of the UPDRS-IV, considered as a dyskinesia scale in patients treated with levodopa (lower part, B). In this latter group the maximal effect was seen after 150 mg and remained stable thereafter.

a placebo-controlled study.[8] (b) The observed effect increased with time, opposite to that expected with placebo, and was clearly different according to the associated therapy: diminishing motor fluctuations but not UPDRS-III in levodopa-treated patients and, conversely, improving motor performance in DA agonist-treated patients. (c) The biochemical data for the levodopa patients group demonstrated an improvement proportional to the increase of serum AUC, a well-known biochemical change capable of reducing motor fluctuations, particularly "off" time and also an objective dose-related finding unlikely explainable as a placebo effect.

Lastly, it can be questioned whether the incremental effect is due to a time effect rather than a dose effect. The reduction in UPDRS-III at the same time point (4 weeks of treatment) with three doses (two extrapolated from study 009 and one from the present study) from baseline was 1.5 points after 40 mg/day, 2.1 at 70 mg/day, and 3.4 after 150 mg/day, strongly suggesting at the same time a clear dose-related improvement. Furthermore, in the present study a decrease of 4.2 UPDRS-III points was reached at week 6, whereas in study 009[8] the lower dose reached a 3-point decrease and the higher dose at 8 weeks. In the present study the highest dose obtained a higher degree of improvement at the same time point, and a similar degree of improvement was reached earlier than with the doses used in the 009 study. These data suggest a dose effect rather than a treatment duration-related effect.

In conclusion, this study demonstrated that safinamide causes a dose-dependent increase of peripheral levodopa comparable to the highest reported in the literature with tolcapone,[15] a potent COMT inhibitor. More experiments are necessary to fully explain the mechanism underlying this finding.

The results also support the hypothesis that MAO-B inhibition is a minor contributor to the symptomatic effect of safinamide in PD. Based on extrapolation from animal data in three species, including primates, glutamate release inhibition

should occur at the doses used, but its exact role is still under investigation. All the clinically available putative anti-glutamate drugs[16-19] have thus far failed to demonstrate motor improvement in clinical trials. However, whether or not these drugs clinically reach a cerebral concentration capable of exerting the anti-glutamate effect that they demonstrated in various experimental paradigms remains unclear. In primates with serum levels lower than those obtained in this study, safinamide is found in the brain at levels higher than the IC_{50} for glutamate release inhibition.[5]

As an add-on to DA agonists, safinamide has confirmed clear improvement on the UPDRS-III. Because the improvement appeared earlier and the observation was terminated before the time at which maximal efficacy has been reported,[8] it seems logical to expect that the doses used in this study may offer greater benefit.

When safinamide was added to levodopa a lesser motor improvement was seen, probably reflecting the pre-existing optimal treatment regimen, but a significant reduction of "off" time without worsening of the dyskinesia scale occurred. Controlled clinical studies have been designed and are ongoing to test these expected improvements in a larger patient population.

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Safinamide as add-on to levodopa improves motor function without worsening dyskinesia in patients with mid-late Parkinson's disease

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INTRODUCTION

- Levodopa is still regarded as the most effective drug for treating the motor symptoms of Parkinson's disease (PD).[1] However, longer-term use is associated with motor fluctuations and dyskinesia,[2] which can impact on patients' quality of life.[3]
- Patients with levodopa-induced motor fluctuations (for example, wearing off) usually require add-on therapy. However, agents that increase dopaminergic function (and therefore have the potential to improve motor function) may exacerbate dyskinesia. For this reason, there is a need for agents with a mechanism of action that extends to non-dopaminergic systems.
- Safinamide is an α-aminoamide in Phase III clinical development as an add-on therapy to dopamine agonists or levodopa. Safinamide has both dopaminergic and non-dopaminergic mechanisms of action, including monoamine oxidase-B (MAO-B) and dopamine reuptake inhibition, activity-dependent sodium channel antagonism, and inhibition of glutamate release *in vitro*.[4-6]

OBJECTIVE

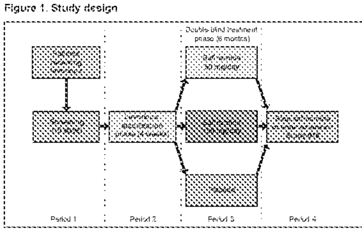
- To evaluate the effect of safinamide as add-on to stable levodopa on motor function and dyskinesia in patients with mid- to late-stage PD experiencing motor fluctuations.

METHODS

Study design

- 24-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group study with four periods: screening, stabilization, treatment, and taper/entry to the long-term extension study (Figure 1).

Figure 1. Study design



Patients

- Male or female patients aged 30 to 80 years with idiopathic PD (>3 years' duration; Hoehn and Yahr Stage I–IV) and motor fluctuations (>1.5 hours' daily OFF time).
- Patients were excluded if they had wide/unpredictable fluctuations or severe, disabling peak-dose or biphasic dyskinesia.

Treatments

- Safinamide 50 mg/day, safinamide 100 mg/day, or placebo as add-on therapy to levodopa.
- The levodopa dose was to remain stable during the 24-week treatment period, if possible.
- Patients on PD therapies other than MAO-B inhibitors were eligible for inclusion, but the dose had to remain stable during the treatment period, if possible.
- If a patient's clinical condition warranted a change (increase or decrease) in the dose of levodopa or other PD therapies (i.e. in the event of clinically significant motor deterioration or adverse events, respectively), all endpoint evaluations were carried out before the change was made.

Assessments

- The primary efficacy endpoint was the change (baseline to Week 24) in mean daily ON time (ON time without dyskinesia plus ON time with minor dyskinesia). This information was recorded by patients in a daily diary.
- Secondary endpoints included the change (baseline to Week 24) in scores for the Unified Parkinson's Disease Rating Scale (UPDRS) Parts III (motor examination) and IV (complications of therapy), and the Dyskinesia Rating Scale (DRS).
- Post hoc analyses on the UPDRS subscale scores were carried out to further evaluate the effect of safinamide on motor function and dyskinesia (Table 1).
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory data, and vital signs.

Motor function	UPDRS items
Bradykinesia	Part II, Items 23–26, 31
Rigidity	Part III, Item 22
Postural instability gait disorder	Part III, Items 13–15, 29, 30
Freezing when walking	Part II, Item 14
Dyskinesia	Part IV, Items 32–34
Dyskinesia and dystonia[a]	Part IV, Items 32–35

[a]Individual scores for Items 32–35 were also evaluated
UPDRS, Unified Parkinson's Disease Rating Scale

Statistical analysis

- Least squares means changes (baseline to Week 24) between active treatment and placebo were compared using a mixed linear model (ON time) and ANCOVA (UPDRS), and Wilcoxon rank sum test (DRS scores).

RESULTS

- In total, 669 patients were randomized to treatment (Table 2) and 594 patients (89%) completed the study.

Characteristic	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Gender, n (%)			
Male	160 (72.1)	157 (70.4)	163 (72.8)
Race, n (%)			
White	42 (18.9)	43 (19.3)	44 (19.6)
Asian	180 (81.1)	180 (80.7)	179 (79.9)
Age, years, mean (SD)	59.4 (9.41)	60.1 (9.67)	60.1 (9.19)
Disease duration, years, mean (SD)	8.2 (3.8)	7.9 (4.0)	8.2 (3.8)
Daily ON time,[a] hours, mean (SD)	9.3 (2.2)	9.4 (2.3)	9.5 (2.4)
Daily OFF time, hours, mean (SD)	5.3 (2.1)	5.2 (2.1)	5.2 (2.2)
UPDRS Part III (motor examination) score, mean (SD)	28.7 (12.02)	27.3 (12.67)	28.3 (13.30)
Daily levodopa dose, mg, mean (SD)	560 (454)	553 (346)	601 (341)

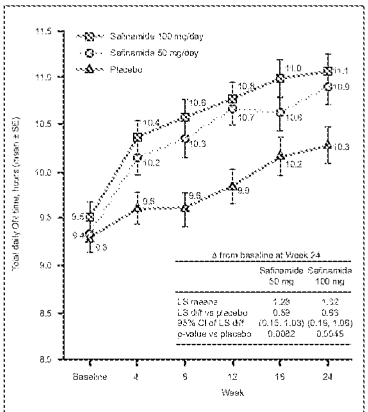
[a]Without dyskinesia or with minor dyskinesia
SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale

- There were no significant differences between the treatment groups for any demographic or disease-related characteristics (Table 2).
- The levodopa dose was to remain stable during the study, but there was a small increase in dose (0.27%) in the placebo group and small decreases in the safinamide 50 and 100 mg/day groups (-1.05% and -2.16%; p=0.016 for safinamide 100 mg/day versus placebo).

Efficacy

- The addition of safinamide to stable doses of levodopa resulted in significant increases in total daily ON time (without dyskinesia or with minor dyskinesia) in both safinamide groups (~1.3 h) versus placebo (0.63 h) (Figure 2). There were no significant between-group differences for the change in ON time with troublesome dyskinesia (+0.2 h for placebo, +0.3 h for safinamide 50 mg/day, and +0.2 h for safinamide 100 mg/day).

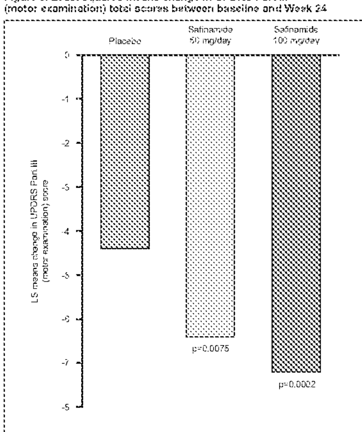
Figure 2. Mean change in ON time (ON without dyskinesia plus ON with minor dyskinesia) during the course of the study



Using an ANCOVA analysis, all time points after baseline were statistically significant when compared with placebo, with the exception of safinamide 50 mg/day at Week 18 (p=0.0739).
CI, confidence interval; LS, least squares; SE, standard error

- Both doses of safinamide were associated with significant improvements in UPDRS Part III (motor examination) scores versus placebo (Figure 3). There were also significant improvements in the UPDRS Part III subscale scores for safinamide 100 mg/day versus placebo (Table 3).

Figure 3. Least squares means change in UPDRS Part III (motor examination) total scores between baseline and Week 24



LS, least squares; UPDRS, Unified Parkinson's Disease Rating Scale

Parameter	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Motor			
UPDRS III, bradykinesia	-1.5	-2.3 (p=0.[illegible])	-2.[illegible] (p=0.0[illegible])
UPDRS III, rigidity	-1.1	-1.5 (p=0.060)	-1.3 (p=0.057)
UPDRS III, postural instability gait disorder	-0.2	-0.2 (p=0.278)	-0.2 (p=0.[illegible])
UPDRS II, freezing when walking	-0.2	-0.2 (p=0.730)	-0.4 (p=0.040)
Dyskinesia			
UPDRS IV, dyskinesia	0.1	-0.1 (p=0.171)	-0.1 (p=0.0828)
UPDRS IV, dyskinesia and dystonia	0.0	-0.1 (p=0.072)	-0.1 (p=0.084)
DRS	-0.2	-0.2 (p=0.2332)	-0.3 (p=0.2743)

DRS, Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale

- There were no statistically significant differences for either dose of safinamide versus placebo for the change in UPDRS Part IV scores for dyskinesia and/or dystonia or for the DRS scores (Table 3).

Tolerability and safety

- Incidences of treatment-related TEAEs were 30% for safinamide 50 mg/day, 29% for safinamide 100 mg/day, and 22.5% for placebo (p=0.209). The rate of discontinuation due to TEAEs was low (5–6%) and similar between treatment groups.
- The most common TEAEs are shown in Table 4. Although dyskinesia was reported as a TEAE more frequently in the safinamide groups versus placebo, it was generally transient and mild or moderate in severity. Furthermore, there were no significant between-group differences for patient-reported ON time with troublesome dyskinesia, or for the physician-rated UPDRS Part IV scores (dyskinesia and/or dystonia) or DRS scores (see Table 3).
- Changes in laboratory values and vital signs were similar between treatment groups.

Event	Placebo (n=222) n (%)	Safinamide 50 mg/day (n=223) n (%)	Safinamide 100 mg/day (n=224) n (%)
Number of patients reporting at least 1 TEAE	150 (67.6)	149 (66.8)	149 (66.5)
Dyskinesia	27 (12.2)	46 (20.6)	40 (17.9)
Worsening PD	18 (8.1)	11 (4.9)	9 (4.0)
Cataract	15 (6.8)	9 (4.0)	14 (6.3)
Back pain	13 (5.9)	10 (4.5)	11 (4.9)
Depression	11 (5.0)	2 (0.9)	4 (1.8)
Headache	10 (4.5)	12 (5.4)	11 (4.9)

PD, Parkinson's disease; TEAE, treatment-emergent adverse event

CONCLUSIONS

- **Based on patient diary data, add-on therapy with safinamide significantly improved ON time with non-troublesome dyskinesia in patients with levodopa-induced motor complications; it also significantly improved overall motor function in these patients.**
- **Dyskinesia reported as a TEAE was more frequent in the safinamide groups than in placebo, but was generally transient and mild or moderate in severity. All other TEAEs were similar in incidence to placebo.**
- **Safinamide was also well tolerated in this population of patients: incidences of TEAEs leading to discontinuation and changes in laboratory and vital-sign data were similar to placebo.**
- **The effects of safinamide as add-on therapy in patients with levodopa-induced motor complications are also being studied in the ongoing SETTLE study (see Poster 378).**

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The Study 016 investigators were:
INDIA: [illegible]
ROMANIA: [illegible]
ITALY: [illegible]

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Conclusion: Case-control studies in genetically homogeneous populations are the most efficient paradigm for the association of genes in complex traits. The homogeneous population of Trondheim, Norway has allowed us to dissect the haplotype structure of the Tau gene and refine the functional variability associated with PD and PSP.

P78

The Nurr1 7048 G 7049 intronic insertion is not associated with Parkinson's disease

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Objective: To establish whether the Nurr1 gene which is critical for midbrain dopaminergic cell development and survival is a risk factor associated with PD.

Backround: Nurr 1 is an orphan nuclear receptor and functions as a transcriptional activator of tyrosine hydroylase and the dopamine transporter gene. Knockout mice do not develop nigral dopaminergic neurones and hetrozygous knockout mice have increased sensitivity to MPTP neurotoxicity. Mutations in exon 1 have been reported to segregate in a dominant manner with familial PD.

A recent study showed that patients with homozygosity for the 7048 G 7049 intronic insertion were 8.4 times more likely to develop PD than those who were homozygous for the wild type allele.They also speculated that this may have had a role in the expression of the gene.

Methods: Our study included 381 cases of PD consisting of 224 sporadic PD cases, 131 of whom were pathologically proven,104 cases of young onset PD and 53 familial cases.We used 231 control samples of whom 160 did not have pathological evidence of PD. Genotyping for the 7048 G 7049 polymorphism was done using the restriction enzyme BseR1 and representative samples were confirmed using direct sequencing.

Results: We did not find any association that reached ststistical signifance between sporadic,YOPD, or fPD and control populations with either hetrozygosity or homozygosity for the Nurr1 polymorphism. The results are displayed below (see Table).

Conclusion: We did not detect the association with Nurr1 as previously reported. There may be several reasons for this including population stratification, differences in the linkage between populations, patient numbers too small to detect modest factors and statistical artefact. Association studies are powerful way to indentify disease susceptibility loci in complex disorders like PD. Further studies using larger numbers, linkage dysequilibrium, and genomically matched controls are needed to establish the role of Nurr1 in PD.

	Controls, n (%)	Total PD, n (%)	Sporadic PD, n (%)	YO PD, n (%)	FPD, n (%)
Wild type	144 (62.3%)	223 (58.5%)	133 (59.4%)	62 (59.6%)	28 (52.8%)
Heterozygous	77 (33.3%)	143 (37.5%)	82 (36.6%)	38 (36.5%)	23 (43.4%)
Homozygous	10 (4.3%)	15 (3.9%)	9 (4%)	4 (3.8%)	2 (3.8%)

P79

Two different phenotypes of the same *Parkin* mutation in a large pedigree

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Objective: To describe two different phenotypes of a *parkin* mutation observed in a large pedigree.

Background: Autosomal recessive juvenile parkinsonsism (AR-JP) has been related to mutations in the *parkin* gene. Genotype-phenotype correlation is not yet determined.

Methods: Members of a large Arabic Muslim Israeli family have been followed for 15 years. Genomic DNA was extracted from blood leukocyts and examined using RFLPs and direct sequencing of all 12 exons of the *parkin* gene.

Results: The consanguinity of the affected branches of the family was established back to the seventh ancestral generation. In the first branch, a deletion of one A at position 202 in exon 2 of *parkin* gene was found. In this branch, four brothers (out of 10 siblings) were affected. Ages of onset were 35, 33, 37, 30 years and the disease duration 27, 22, 9 and 14 years. The onset and subsequent progression of parkinsonian symptomatology were similar for all four patients. Hand tremor was the first symptom; later bradykinesia and rigidity were observed. Additionally, all presented postural hand tremor. A maternal aunt who suffered only of postural tremor (onset 60 years) was found heterozygous for the same mutation. The second branch of the family (2 first-degree cousins affected) also carried an A deletion at position 202 in exon 2. The clinical picture was different and dominated by axial dystonia. The age of onset of the female patient was 23 years (duration of disease 40 years). The initial symptom was rest tremor in the upper limbs and difficulty in walking. Few years later, camptocormia occurred which progressed gradually up to the development of permanent 90 degrees forward trunk flexion. The male patient's disease onset was at the age of 19 years (duration of disease 17 years) with tremor in upper and later lower limbs, followed by rigidity and bradykinesia. He later developed axial dystonia expressed by scoliosis. Levodopa response was excellent for all patients. The total daily dose remained low (<500 mg) for up to 30 years. The axial symptoms of the second branch patients were levodopa responsive.

Conclusions: A *parkin* mutation was expressed by different phenotypes in a large pedigree. Axial dystonia may represent a major symptom in these patients. Postural tremor might be the expression of heterozygous mutations in *parkin* gene suggesting that gene dosage might influence the age at onset and phenotype of AR-JP.

P80

A 2-year, multicenter, placebo-controlled, double-blind, parallel-group study of the effect of riluzole on Parkinson's disease progression

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Objective: To assess if riluzole can slow the progression of Parkinson's disease (PD) in patients with early disease.

Background: Riluzole, a blocker of glutamatergic neurotransmission and sodium channels, has been shown to extend survival and/or time to tracheostomy in patients with amyotrophic lateral sclerosis. It also reduces 6-OH-DA and MPTP toxicity in various in vivo models of parkinsonism in rodents and monkeys.

Methods: This was a 2-year placebo-controlled, double-blind parallel study assessing the capacity of 2 doses of riluzole (50 mg b.i.d. or 100 mg b.i.d.) over 2 years to delay the progression of signs and symptoms of PD as determined by the ability of the drug to delay the initiation of levodopa or a dopamine (DA) agonists (primary endpoint) in untreated patients with early PD. Secondary endpoints were worsening of clinical symptoms assessed using the UPDRS after a 2-month wash-out at the end of the study, and functional integrity of striatal dopamine nerve terminals as measured with ^{18}F-Dopa PET scanning. Safety data were monitored throughout the study. Log-rank test in ITT population was used to compare time to levodopa or DA agonist between combined-riluzole and placebo groups (primary analysis). An interim analysis was planned after one third of the patients had reach 2 years of follow-up to propose early termination if there was not a reasonable possibility of success if the study were continued (futility analysis).

Results: 1084 PD patients were randomized (62.6 yr, 61% males, 17 months of disease duration). At interim analysis the predefined futility criteria were met. Then, the study was terminated prematurely, due to lack of efficacy. At the time of final analysis, 711/1084 patients had started levodopa or DA agonist. The probability of starting levodopa or DA agonist during the first 18 months was 0.69 on placebo and 0.71 on riluzole (Hazard Ratio 1.07; 95% CI 0.91–1.26, P 0.41). There was no difference on secondary endpoints. AES were similar to that observed in previous studies and were more frequent on riluzole than on placebo.

Conclusion: Riluzole did not show superiority over placebo on PD progression.

Effect of safinamide on depressive symptoms in patients with mid-late stage Parkinson's disease

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INTRODUCTION

- Depression is common in Parkinson's disease (PD) an estimated 35% of patients have clinically significant depressive symptoms, while 17% have major depressive disorder.[1] Depression is associated with poor quality of life;[2,3] it also has a negative impact on patients' ability to function[4] and increases caregiver burden.[2] PD therapy should, therefore, be focused on improving both motor and depressive symptoms.
- The precise pathology underlying depressive symptoms in PD is not known, but data suggest that both dopaminergic and non-dopaminergic mechanisms are involved.[5,6]
- Safinamide is an α-aminoamide in development for use in PD that has both dopaminergic and non-dopaminergic mechanisms of action.[7,8]

OBJECTIVE

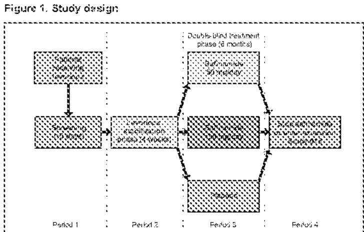
- The efficacy and safety of safinamide as add-on therapy to stable levodopa were assessed in a Phase III trial in patients with mid- to late-stage PD and motor fluctuations. Here, we describe data on the effect of safinamide on symptoms of depression in study participants.

METHODS

Study design

- 24-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group study with four periods: screening, stabilization, treatment, and taper/entry to the long-term extension study (Figure 1).

Figure 1. Study design



Patients

- Male or female patients aged 30 to 80 years with idiopathic PD (>3 years' duration) and Hoehn and Yahr Stage I–IV.
- Patients with motor fluctuations (>1.5 hours' daily OFF time). Patients were excluded if they had wide/unpredictable fluctuations or severe, disabling peak-dose or biphasic dyskinesia.
- Patients with depression, defined as a GRID Hamilton Rating Scale for Depression–17-item (GRID HAM-D) total score >17, were also excluded.

Treatments

- Once-daily single dose of safinamide 50 mg/day, safinamide 100 mg/day, or placebo as add-on therapy to levodopa.
- The levodopa dose was to remain stable during the 24-week treatment period, if possible.
- Patients on PD therapies other than monoamine oxidase-B inhibitors were eligible for inclusion, but the dose had to remain stable during the treatment period, if possible.
- If a patient's clinical condition warranted a change (increase or decrease) in the dose of levodopa or other PD therapies (i.e. in the event of clinically significant motor deterioration or adverse events, respectively), all endpoint evaluations were carried out before the change was made.

Assessments

- The primary efficacy endpoint was the change in mean daily ON time (ON time without dyskinesia plus ON time with minor dyskinesia) recorded in patient diaries. Other efficacy variables included changes in the GRID HAM-D total score and the patient-rated 'emotional wellbeing' subscale of the PD Questionnaire (PDQ-39).
- The following post hoc analyses were carried out:
  - GRID HAM-D item scores
  - Change in GRID HAM-D total score according to baseline score (<10 and ≥10) and antidepressant use.
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory data, and vital signs.

Statistical analysis

- Least squares (LS) means changes (baseline to Week 24) between active treatment and placebo were compared using a mixed linear model (ON time) and ANCOVA (other efficacy endpoints).

RESULTS

- In total, 669 patients were randomized to treatment (Table 1) and 594 patients (89%) completed the study.
- There were no significant differences between the treatment groups for any demographic or disease-related characteristics (Table 1).

Characteristic	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Gender, n (%)			
Male	160 (72.1)	157 (70.4)	163 (72.8)
Race, n (%)			
White	42 (18.9)	43 (19.3)	44 (19.6)
Asian	180 (81.1)	180 (80.7)	178 (79.0)
Age, years, mean (SD)	59.4 (9.41)	60.1 (9.67)	60.1 (9.19)
Disease duration, years, mean (SD)	8.3 (3.76)	7.9 (3.95)	8.2 (3.79)
Daily ON time,* hours, mean (SD)	9.3 (2.15)	9.4 (2.25)	9.5 (2.43)
Daily OFF time, hours, mean (SD)	5.3 (2.06)	5.2 (2.08)	5.2 (2.16)
GRID HAM-D total score, mean (SD)	5.9 (3.79)	6.5 (3.70)	6.0 (3.55)
PDQ-39 emotional well-being score, mean (SD)	30.4 (18.29)	31.1 (19.70)	30.8 (16.86)

*Without troublesome dyskinesia
GRID HAM-D, GRID Hamilton Rating Scale for Depression–17-item;
PDQ-39, Parkinson's Disease Questionnaire; SD, standard deviation

Efficacy

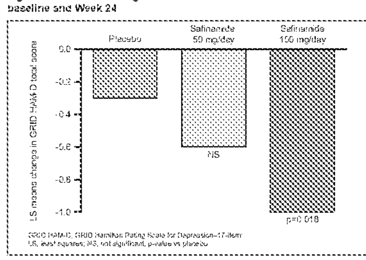
- The addition of safinamide to stable doses of levodopa resulted in significant increases in total daily ON time without troublesome dyskinesia in both safinamide groups versus placebo (Table 2).

Characteristic recorded	Safinamide 50 mg/day		Safinamide 100 mg/day	
	Difference vs placebo (hours/day)	p-value	Difference vs placebo (hours/day)	p-value
ON time without dyskinesia	0.5	0.0367	0.7	0.0079
ON time with minor dyskinesia	0.0	0.9196	-0.1	0.5661
ON time with troublesome dyskinesia	0.1	0.5324	0.0	0.9931
OFF	-0.6	0.0022	-0.6	0.0027
Asleep	0.1	0.5921	0.0	0.6727

Least squares (LS) means and p-values were calculated from an ANCOVA model based on the change from baseline to endpoint, with the baseline value as a covariate

- The improvement in GRID HAM-D total score was significantly greater for safinamide 100 mg/day versus placebo (Figure 2).

Figure 2. LS means change in GRID HAM-D total score between baseline and Week 24



GRID HAM-D, GRID Hamilton Rating Scale for Depression–17-item
LS, least squares; NS, not significant, p-value vs placebo

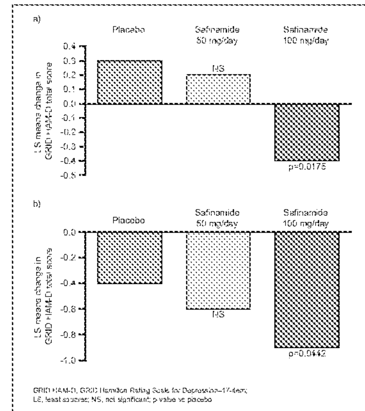
- Improvements in GRID HAM-D item scores for early insomnia, work and activities, and somatic anxiety were also significantly greater for safinamide 100 mg/day versus placebo; depressed mood and loss of appetite were of borderline significance (p=0.0561 and p=0.0584, respectively) (Table 3).

GRID HAM-D item	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Depressed mood	-0.1	0.0	-0.2†
Guilt	0.0	-0.1	0.0
Suicide	0.0	0.0	0.0
Insomnia, early	0.0	0.0	-0.1*
Insomnia, middle	0.1	0.1	0.0
Insomnia, late	0.0	0.0	0.0
Work and activities	0.1	0.0	-0.1*
Psychomotor retardation	-0.1	-0.1	-0.1
Psychomotor agitation	0.0	0.0	-0.1
Anxiety, psychic	-0.1	-0.1	-0.1
Anxiety, somatic	0.0	-0.1†	-0.1**
Loss of appetite	-0.1	-0.1	0.0†
Somatic symptoms, general	0.0	0.0	0.0
Sexual interest	0.0	-0.1†	0.0
Hypochondriasis	0.0	0.0	0.0
Loss of weight (medical history)	0.0	-0.1	0.0
Loss of weight (psychiatrist rating)	0.1	0.2	0.1
Insight	0.0	0.0†	0.0

†p<0.1; *p<0.05; **p<0.01 vs placebo
Data rounded to one decimal place
GRID HAM-D, GRID Hamilton Rating Scale for Depression–17-item; LS, least squares

- Safinamide 100 mg/day was also associated with a significantly greater improvement in the emotional wellbeing subscale of the PDQ-39. LS means changes from baseline were -1.5 in the placebo group, -2.5 in the safinamide 50 mg/day group, and -5.0 in the safinamide 100 mg/day group (p=0.4236 and p=0.009 versus placebo, respectively).
- Most patients (>80%) had a baseline GRID HAM-D total score <10 (184/222 patients in the placebo group, 185/223 patients in the safinamide 50 mg/day group, and 187/224 patients in the safinamide 100 mg/day group) and >90% were not taking antidepressants (205, 206, and 213 patients, respectively). In both subgroups, LS means change in score at Week 24 was significantly greater for safinamide 100 mg (but not 50 mg/day) versus placebo (Figure 3). Between-group differences for the other subgroups (GRID HAM-D ≥10 and antidepressant use) were not significant.

Figure 3. LS means change in GRID HAM-D total score between baseline and Week 24 in (a) patients with a GRID HAM-D score <10 at baseline and (b) not taking antidepressants at baseline



GRID HAM-D, GRID Hamilton Rating Scale for Depression–17-item;
LS, least squares; NS, not significant; p-value vs placebo

Tolerability and safety

- Incidences of TEAEs were 30% for safinamide 50 mg/day, 29% for safinamide 100 mg/day, and 22.5% for placebo (p=0.209). The rate of discontinuation due to TEAEs was low (5–6%) and similar between treatment groups.
- Depression was reported as a TEAE in fewer patients in both safinamide groups compared with placebo. Although dyskinesia was reported as a TEAE more frequently in the safinamide groups versus placebo, it was generally transient and mild or moderate in severity. The most common TEAEs are shown in Table 4.
- Changes in laboratory values and vital signs were similar between treatment groups.

Event	Placebo (n=222) n (%)	Safinamide 50 mg/day (n=223) n (%)	Safinamide 100 mg/day (n=224) n (%)
Number of patients reporting at least 1 TEAE	150 (67.6)	149 (66.8)	149 (66.5)
Dyskinesia	27 (12.2)	46 (20.6)	40 (17.9)
Worsening PD	18 (8.1)	11 (4.9)	9 (4.0)
Cataract	15 (6.8)	9 (4.0)	14 (6.3)
Back pain	13 (5.9)	10 (4.5)	11 (4.9)
Depression	11 (5.0)	2 (0.9)	4 (1.8)
Headache	10 (4.5)	12 (5.4)	11 (4.9)

PD, Parkinson's disease; TEAE, treatment-emergent adverse event

CONCLUSIONS

- **In PD patients with levodopa-induced motor fluctuations and without clinical depression, safinamide 100 mg/day significantly improved both motor symptoms and depressive symptoms rated by physicians and patients. Depression was also reported less frequently as a TEAE in both safinamide groups versus placebo.**
- **Safinamide was also well tolerated in this population of patients: incidences of treatment-related TEAEs, TEAEs leading to discontinuation, and changes in laboratory and vital-sign data were similar to placebo.**
- **Depressive symptoms are also being studied in the ongoing MOTION and SETTLE studies, which are evaluating the efficacy and safety of safinamide as add-on therapy to dopamine agonists and levodopa, respectively, in patients with PD (see Posters 319 and 378).**

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